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Clinical Proceedings

OF THE CHILDREN'S HOSPITAL

WASHINGTON, D. C.

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190 (sick & well infants)	Henrickson[3]	Satisfactory results. Average hospital stay: 5.5 days; average daily weight gain: 3 ounces.

*Maltose-dextrins formula modifier, Mead Johnson

1. Hatfield, M. A.; Simpson, R. A., and Jackson, R. L.: J. Pediat. 44: 32-45 (Jan.) 1954. 2. Frost, L. H., and Jackson, R. L.: J. Pediat. 39: 585-592 (Nov.) 1951. 3. Henrickson, W. E.: GP 8: 51-56 (Oct.) 1953. 4. Litchfield, H. R.: Arch. Pediat. 61: 617 (Dec.) 1944.

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Renal Tubular Acidosis

Discussion by: LEONARD B. BERMAN, M.D.*
Case report by: WELLINGTON HUNG, M.D.† and
LETICIA U. TINA, M.D.‡

When the physician is faced with the combination of rickets and nephrocalcinosis, the differential diagnosis is narrowed very sharply to one of the renal tubular disorders. The following case is a typical example of one such disorder called tubular acidosis. The diagnosis and treatment are discussed and a brief classification of renal tubular disorders is presented.

CASE REPORT

This was the first Children's Hospital admission for this 12 year old white boy who entered on July 14, 1958, with the chief complaint of being of small size all his life. The patient was the product of a normal full term spontaneous delivery. His growth for the first year of life had been normal but the mother noticed during his second year that he was not keeping pace with her other five children. In 1950, at age 4, the patient was hospitalized elsewhere with bronchopneumonia. The mother was told that the child had rickets and she was instructed to administer cod liver oil for two years, which she did. The exact dosage he received, however, is not known. In the same year, when drainage from the left ear developed, the patient was seen by a pediatrician who also noted his small size. Since that time the patient had not been seen by a physician until approximately one month prior to the present admission. He had, however, been noted to be limping while running or walking for at least one year; this limping had increased in the nine months prior to admission. He complained of a mild pain on the outer aspects of both ankles during running and walking for the six months prior to admission, and had always had difficulty in keeping up with other children in sports. He denied muscular weakness. At age 5 the parents began to order specially made clothes because of his small size, and on entering school he weighed only 42 pounds. At the time of this admission to the hospital he weighed 46 pounds and was in the sixth grade.

The patient was breast fed for the first three months of life, after which he was fed an evaporated milk formula for approximately one year. He received vitamins for the first few months of life but did not receive any further vitamins until 1950 after which time he had cod liver oil for a period of two years. Since that time he had not received any additional vitamins. He had drunk chocolate milk and eaten milk products. He stated that he did not drink white milk because it upset his stomach. Dentition first occurred at age 6 months; he sat alone at 7 months, and walking began at 12 months. He had received all the routine childhood immunizations. The only childhood disease had been rubella at age 10. His mother stated that the child voided light colored urine hourly during the day and had done so as long as she could remember; it was also necessary for him to get up between one and two times every

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TABLE 1

Results of Urinalyses and Serum Electrolyte Determinations Prior to Therapy

Dates:	7-14	7-16	7-18	7-21
Urinalyses				
pH	7.0	6.0		6.5
Specific Gravity	1.001	1.001		1.006
Protein	20 mg/100 ml.	20 mg/100 ml.		10 mg/100 ml.
WBC	3–7/HPF	2–4/HPF		3–5/HPF
RBC	1–3/HPF	Occasional		0–2/HPF
Serum Sodium	138 mEq/L	146 mEq/L	145 mEq/L	
Serum Potassium	2.8 mEq/L	4.2 mEq/L	2.8 mEq/L	
Serum Chloride	108.2 mEq/L	127 mEq/L	123 mEq/L	
Serum Calcium	10.6 mg/100 ml.	8.2 mg/100 ml.		
Serum Phosphorus	2.6 mg/100 ml.	1.9 mg/100 ml.		
CO_2 Combining Power	9.6 mEq/L	5.9 mEq/L	8.6 mEq/L	

FIG. 1. X-ray of the upper extremities before treatment showing rachitic deformities at the distal ends of radius and ulna.

FIG. 2. Calcium deposition outlining the renal papillae

night to void. There was no history, however, of ever having had a urinary tract infection or any other urinary difficulties.

The mother was aged 50, living and well, and the father aged 52, living and well. Two sisters, aged 27 and 18 years, and three brothers, aged 25, 23, and 15 years, were all living and well. All siblings were normal in size. There was no history of genito-urinary disease or difficulty in any member of the family.

On physical examination, the patient's temperature was 98.6°F.; pulse rate 88 per minute; respirations 22 per minute; and blood pressure 90/55. His weight was 45 pounds 12 ounces, and his height 47 inches. He appeared as an underdeveloped and fairly well nourished boy who was definitely small for his chronological age. His intelligence appeared to be high normal. His head was symmetrical in shape. The ocular lenses were clear, and the fundi were normal. The left tympanic membrane was perforated and exuded a slight serous discharge. The teeth appeared normal. He was barrel chested and had a slight rachitic rosary, a pigeon-breast deformity, and a definite Harrison's groove. The lungs were clear. The heart was normal. There were no gross deformities of the spine. The abdomen was soft and slightly protuberant; liver, spleen and kidneys were not felt and there were no palpable masses, scars or tenderness. The skin had good turgor. There was a bilateral genu valgum deformity. His knees and wrists were prominent.

Blood and urine chemical determinations during hospitalization are shown in table 1. X-rays of the extremities showed the classical abnormalities of rickets (fig. 1).

FIG. 3. X-ray of upper extremities during treatment showing healing rickets after 3½ months of therapy.

TABLE 2

Serum Electrolyte Determinations after Institution of Therapy

Dates:	9-4	10-9	11-7
Serum Sodium	140 mEq/L	139 mEq/L	139 mEq/L
Serum Potassium	5.6 mEq/L	5.1 mEq/L	5.6 mEq/L
Serum Chloride	115 mEq/L	108 mEq/L	106.2 mEq/L
Serum Calcium	9.7 mg/100 ml.		11.4 mg/100 ml.
Serum Phosphorus	5.6 mg/100 ml.		6.0 mg/100 ml.
CO_2 Combining Power	18.6 mEq/L	20.3 mEq/L	19.5 mEq/L

Intravenous pyelogram demonstrated a collection of stippled calcifications which were clustered around the minor calyces (fig. 2).

The patient was treated and subsequently discharged from the hospital on the following therapy: Sodium citrate-citric acid mixture (Shohl's mixture)—20 cc. three times a day; vitamin D—50,000 U.S.P. units daily and potassium gluconate (Kaon® elixir)—20 milliequivalents four times a day.

Roentgen studies of the long bones three months after discharge showed striking improvement (fig. 3). There was no remarkable change noted in the renal calcification. Post-treatment laboratory findings are summarized in table 2.

There was considerable improvement in the child's general condition. He had gained 10 pounds in weight and was taller by one-half inch. He no longer suffered from leg pains and was able to walk and run comfortably. Polyuria persisted but was less than before. He has continued to take the sodium citrate-citric acid mixture, but the vitamin D was discontinued on October 28, 1958, and the potassium supplement was reduced to 10 milliequivalents four times a day.

DISCUSSION

Primary tubular disorders are due either to congenital or acquired causes. The congenital biochemical disorders affecting tubules are particularly interesting since they are genetic diseases, i.e., diseases in which a gene is defective. This defective gene leads to a missing or defective enzyme which is thus unable to carry on its normal metabolic function.

In deciding what kinds of tubular disorders are possible, it should be noted that a renal tubule has a limited number of mechanisms for changing the glomerular filtrate that passes through it. It can remove solutes from the filtrate (reabsorption), or add solutes to the filtrate (secretion) (fig. 4). Abnormalities originating primarily in the tubular cell can therefore be divided into those of excessive or deficient reabsorption or secretion. There are not as yet diseases to go with all these possibilities. No *primary* abnormality of excessive secretion is known, although one of the effects of hyperaldosteronism is excessive secretion of potassium into the urine. Deficient secretion is possibly exemplified by deficient hydrogen ion excretion into the tubular lumen, as will be discussed in the present case. Excessive reabsorption does not occur as a primary abnormality. Deficient reabsorption, of course, occurs in a great variety of diseases. Reabsorption in the tubule is such a multifaceted process and is concerned with so many specific enzymes that it is quite possible to have single or multiple absorptive defects, all very separate from one another.

Deficient reabsorption in the renal tubule may arise in several ways (fig. 5). There may be, for example, a genetically determined tubular intracellular enzyme defect which results in impaired transport of sugar, amino acids, or any one of a number of substances. On the other hand, there may be a renal tubule which is unresponsive to a specific hormone. If the antidiuretic hormone is involved, water fails to be reabsorbed normally. If the parathyroid hormone is involved, a syndrome called pseudohypoparathyroidism arises.

Tubular defects also arise in other ways. In galactosemia the accumulation of galactose is apparently nephrotoxic since amino acid reabsorption is impaired. Finally, the tubular cell may be directly involved by a disease or a drug. Pyelonephritis, carbon tetrachloride, and chlorothiazide all change renal tubular reabsorption in various ways.

In the case presented, a child with rickets and nephrocalcinosis is losing

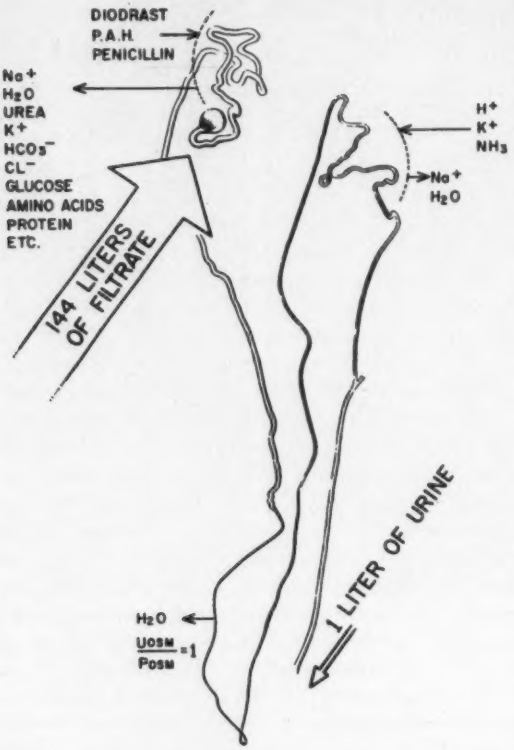

FIG. 4. Schematic representation of nephron function. The volumes shown are adult figures.

a certain combination of substances in his urine because of failure of tubular reabsorption. That combination includes bicarbonate, calcium, phosphorus, potassium, sodium, and water. Loss of bicarbonate leads to an alkaline urine and a relatively acid blood. In addition, there is a reabsorption of chloride in excessive amounts for reasons poorly understood; this results in a hyperchloremia. The systemic acidosis leads to a loss of calcium in the urine, and the presence of calcium in an alkaline urine results in nephrocalcinosis. Furthermore, the excess anion loss leads to excess loss of potassium and sodium, as well as calcium. These losses, in turn, have secondary effects. Hypercalcuria, for example, produces a lack of response to antidiuretic hormone which leads to polyuria. Polydipsia, dehydration and inability to concentrate the urine may follow. Failure to reabsorb phos-

a) Genetic defect → renal tubular intracellular enzyme defect → impaired transport
b) Genetic defect → non-renal metabolic defect → accumulation of abnormal metabolites → impaired transport
c) Genetic defect → renal tubular cell unresponsiveness to a hormone → impaired transport
d) Renal disease or nephrotoxic agent → tubular cell injury → impaired transport

FIG. 5. Primary and secondary defects of tubular dysfunction

phorus is an important and poorly understood part of the syndrome. The resultant combination of reabsorptive defects leads to an alkaline urine, an acid blood, nephrocalcinosis and lithiasis, rickets (and osteomalacia in the adult), skeletal muscle paralysis due to hypokalemia, and dehydration.

The pretreatment laboratory data in this boy are compatible with the foregoing description. His serum sodium levels were normal since it is possible to lose a great deal of sodium in the urine without changing the serum concentration. His serum potassium level was, on two out of three occasions, unequivocally low. His serum chloride level was also high and his serum calcium was normal. The serum phosphorus on two occasions was low, reflecting the large amounts of phosphorus lost in the urine. It is not known whether a defective phosphorus reabsorption mechanism is part of this disease or if there are alternative explanations. His carbon dioxide combining power was compatible with a severe metabolic acidosis. Urine pH on three occasions was 7.0, 6.0, and 6.5. An alkaline urine is considered to be one of a pH of 6.0 or above; his urine is therefore alkaline. This child has all of the blood chemical findings, all the urinary findings, and all the bone findings of a boy who cannot acidify his urine, i.e., all of the diagnostic features of tubular acidosis.

Tubular acidosis has been called by many different names including Lightwood's disease and Albright's disease. Most authorities prefer, however, to call it tubular acidosis which means a disease of the renal tubule that results in a systemic acidosis.

What is the defect in acidification of the urine in this condition? In the normal child, carbon dioxide diffuses very easily into the renal tubular cell, and together with water immediately forms carbonic acid under the influence of carbonic anhydrase. This carbonic acid breaks down into bicarbonate and hydrogen ions. The hydrogen ion, when excreted into the urine, has several fates: It may meet with bicarbonates and form carbonic acid, it may be buffered by phosphate, or it may be buffered by ammonia to form the ammonium ion which then combines with a chloride ion to produce ammonium chloride. All these processes enable the body to excrete the hydrogen ion load which it must rid itself of every day. Normally, all serum bicarbonate is filtered through the glomerulus; 85 per cent of this

amount is reabsorbed through the proximal tubule. The remaining 15 per cent is carried to the distal tubule to combine with hydrogen ions to form carbonic acid. In the patient with tubular acidosis, there are two possible abnormalities. There may be excessive amounts of bicarbonate in the urine due to a *diminished hydrogen ion secretion* or *diminished bicarbonate reabsorption*. In either case the patient has a persistently alkaline urine and all the other consequences enumerated above.

Problems in treatment of this condition include rickets, hypokalemia, polyuria, acidosis, and nephrocalcinosis. Since both bicarbonate and potassium are deficient, potassium citrate is a useful drug in treatment. Vitamin D in amounts sufficient to correct the rickets is advised by some authorities and condemned by others. It must be administered cautiously in view of the nephrocalcinosis. Polyuria may be a function of calcium and potassium losses. It may cease with recovery of concentrating ability during treatment. The urine remains alkaline since we cannot reverse the congenital biochemical defect responsible for the alkalinity. Pyelonephritis may be expected in the presence of nephrocalcinosis, and must be treated vigorously to preserve maximal renal function.

Prophylaxis of Rabies

KARL HABEL, M.D.*

Recent developments in the prophylaxis of rabies have been directed toward the solution of three problems. The first of these is to increase the efficacy of the specific prophylaxis in man; the need for this has been that the usual methods of prophylaxis have not been sufficient when the patient has been severely bitten by a rabid animal. The second and of almost equal importance in this country is to reduce the hazard from rabies prophylaxis in man, because reactions to the treatment itself, although infrequent, are dangerous. Last is the protection of special groups such as veterinarians, dog catchers, and mailmen who are frequently exposed to the bites of animals.

Undoubtedly the key development in increasing the efficacy of prophylaxis in man in recent years has been the use of rabies antiserum along with a course of vaccine. This procedure is now recommended by practically all workers in the rabies field.

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Experimentally, when guinea pigs were given street virus intramuscularly to simulate what happens in man, and vaccine treatment was started after the infection, it was very difficult to protect the animals; most of them died as did the control animals. When a dose of antiserum was given by itself, there was a definite reduction in mortality, much better than with vaccine alone, but when a single dose of antiserum was combined with a course of vaccine, the best results of all were obtained. The reason that the combination is effective is that the antiserum markedly prolongs the incubation period although it usually does not prevent eventual death. However, in the vaccine prophylaxis of rabies, we are trying to actively immunize a person against a virus after the virus is already in the body. Active immunization takes time; and therefore the length of the incubation period is very important in rabies prophylaxis and is probably the only reason why vaccine is effective at all. Therefore, a combination of antiserum to prolong the incubation period with vaccine to produce an active immunity should give us better results than either of these two methods alone.

After many animal experiments, the use of rabies antiserum combined with a course of vaccine was finally tested in humans under field conditions in Iran. Seventeen people in a village were attacked and bitten on the head and neck by a rabid wolf. These patients were divided into three treatment groups at the Pasteur Institute in Teheran where they arrived within 31 hours of the attack. Group A received two doses of antiserum given on days one and five, and vaccine every day for 21 days; of 5 patients treated in this manner there were no deaths due to rabies. Group B received only a single dose of antiserum along with a 21 day course of vaccine; there was one death due to rabies among 7 patients. A particularly unusual case was a 10 year old boy who was unconscious when he arrived for treatment because the wolf had bitten him completely through both tables of the skull, giving him what amounted to an intracerebral injection of rabies infected saliva. He was given antiserum every other day for six doses and also a course of vaccine, and he survived. Group C was treated in the usual way with a course of vaccine only, and 3 out of 5 of these patients died of rabies. The mortality rate in this last group confirmed the past experience of the Pasteur Institute in Teheran where people bitten on the head and neck by rabid wolves had a mortality rate between 40 and 50 per cent in spite of "adequate" vaccine treatment. Even though this is a small series, and thus of questionable statistical significance, the combined mortality of those who were treated with any amount of antiserum and vaccine combined, when compared with the mortality of the group that had vaccine alone, certainly suggests that a combination of antiserum and vaccine is more efficacious than vaccine alone in preventing rabies after severe exposure.

In order to study rabies antibody production in a quantitative way normal human volunteers not exposed to rabies have been used. These individuals have been given various schedules of vaccine with or without a dose of antiserum. Blood was obtained at various stages of treatment and tested quantitatively for rabies antibodies. In one group only seven doses of vaccine were given. (Actually there are places in the world, for example, Yugoslavia, where this is the routine treatment for mild exposure to rabies.) When the serums of these individuals were tested, a slight antibody response was detected on the tenth day which rose higher on the fourteenth day, was very high on the twenty-first day, and was just beginning to fall on the twenty-eighth day. When a single dose of antiserum was given intramuscularly to another group, there was a detectable level of antibody in their serums on the very first day. This antibody was still present on the third day, but the level was definitely falling by the fifth day, and at 28 days, there was a just barely detectable level. When antiserum and vaccine were given together, the immediate rise of passive antibody occurred, but these patients, unlike the group that received vaccine alone, did not get an active antibody response later. Their antibody response was almost exactly the same as the group that had gotten antiserum alone. This is evidence that the antibody in the antiserum is interfering with the antigenicity of the vaccine being given at the same time.

Another group received both antiserum and vaccine, but vaccine was given for 12 days instead of seven; this group demonstrated an early rise of antibody due to the passive antibody in the antiserum, but they also had a late antibody response which was an active response to the antigen of the vaccine after the passive antibodies of the antiserum had been dissipated. On this basis, we still recommend the use of antiserum and vaccine for severe exposures to rabies, but we modify this by advocating that all the antiserum be given in a single dose as early as possible after exposure. Furthermore, when antiserum is combined with vaccine, we recommend never giving less than 14 daily doses of vaccine; we have found that 12 to 14 doses of vaccine will produce an active antibody response and overcome any interference by the passive antibody. Conversely, the passive antibody is not interfered with by the antigen in the vaccine.

In considering the techniques of rabies prophylaxis, proper local treatment of the wound should not be forgotten; *every bite wound should be treated on the basis that it might possibly represent an exposure to rabies.* First of all, it has been shown experimentally that the fuming nitric acid treatment which has been recommended in textbooks for many years as a specific treatment for rabies introduced into bite wounds can certainly be questioned. One of the chief reasons for questioning this procedure is that it is a rare practicing physician who has fuming nitric acid on his medicine shelf;

why recommend something that is never available? In addition, it has been shown experimentally that fuming nitric acid does not give any better and sometimes not as good results as ordinary methods of treatment of wounds, namely, the flushing of the wound with large amounts of soapy water. Experiments done on animals by Shaughnessy indicate that 1:1000 Zephiran Chloride® applied by swab into the bite wound is as good as the flushing with soapy water, and as good or even better than fuming nitric acid. In the World Health Organization Committee on Rabies, we do not say that fuming nitric acid is contraindicated; however, we do say that it is not particularly important to use it for the ordinary type of wound. We still do recommend it for the puncture type where it is impossible to flush out the bottom of the wound. Here we recommend the use of fuming nitric acid applied by a metal applicator which can be introduced to the depth of the puncture wound.

Experimentally, the most effective local treatment of a wound is specific treatment, the introduction of antiserum directly into the site where the virus has been introduced. Certainly if there is any situation in human medicine where passive prophylaxis is indicated, it is in rabies, because there is probably no other situation in human infectious disease where we know the exact minute of exposure, the exact place where the virus is introduced and the exact individual, in most cases, who did the exposing.

Do we recommend that antiserum be infiltrated in and around every bite wound on the basis that it might be a rabies exposure? The obvious answer is "no." We recommend the use of antiserum locally only when there is no doubt that this represents an exposure to rabies, such as when the animal that has done the biting is obviously rabid clinically or by laboratory tests at the time that we are consulted about local prophylaxis of the bite wound. When we give antiserum along with vaccine as a general prophylaxis, we merely subtract from the total dose the amount we inject locally and inject the rest of it intramuscularly. The amount recommended to be injected locally depends upon where the wound is. It is obviously impossible to infiltrate a bite on the finger with the same amount of antiserum that could be infiltrated around a bite on the leg. From a practical standpoint, we recommend injecting up to 5 ml. This is subtracted from the total dose of antiserum used as a general rabies prophylaxis which is 0.5 ml. per Kg. of body weight.

Unfortunately, rabies vaccine as it has continued to be produced through the years represents the crudest biological material that we inject into human beings by means of a hypodermic needle. It is in most instances a 20 per cent suspension of ground-up brain of a rabbit that has had rabies, and that brain suspension has been treated by some method to kill the virus. Since this suspension is composed of animal tissue, it has species-specific

protein in it; more important, however, is the fact that this tissue is central nervous system tissue.

On this basis there appear to be two kinds of reactions to rabies vaccine based on which antigen is involved. One is the species-specific type of reaction due to sensitivity to the serum protein in the vaccine. In this country, all vaccine for human use, with one exception, is made from rabbit brain. In other parts of the world, it is made from brain of sheep, horses, and other animals. This type of reaction does not occur very often. When it does, it is usually during a second or subsequent course of immunization with the same type of vaccine, and it usually occurs right after the first dose of the subsequent course. Clinical manifestations may be urticaria, respiratory difficulty, fever, nausea, vomiting, or headache. When this type of reaction occurs, we merely change to a vaccine made from some other species. In this country, the vaccine which is given to dogs to protect them against rabies is made from the brain of sheep or horses, and there are other types of vaccine made from chicken-embryo-grown rabies virus. For human use now there is duck-embryo vaccine.

The other type of reaction to rabies vaccine is a more serious one and is not so easily treated. That is the type based on allergy developing to the organ-specific antigen, the brain tissue in the vaccine. As a result of experimental work in the last five to seven years, animals can be made allergic to their own brain. From the pathology and symptomatology that develop in these animals, it is obvious that the so-called allergic or postvaccinal encephalitis following vaccination with rabies vaccine is undoubtedly due to a sensitivity to the brain tissue in the vaccine which causes destructive demyelinating lesions in the central nervous system. This organ-specific antigen will cause reactions in the same as well as different species. For example, allergic encephalitis in guinea pigs can be produced by injecting either rabbit brain or guinea pig brain. The importance of this type of reaction is obvious. Postvaccinal paralysis or encephalitis occurs in approximately one of every 3,000 people who receive a course of rabies vaccine made from brain tissue. In this country today, 60,000 or more people receive rabies vaccine every year. We can therefore expect as many as 20 cases of this type of reaction each year; furthermore, about ⅓ of the cases of brain tissue reaction to rabies vaccine are fatal. There are less than 5 cases of rabies occurring in human beings in this country every year so that we have more cases of reaction to the vaccine than we have cases of rabies itself.

What can be done to avoid this type of reaction? The first thing we emphasize is that no rabies vaccine should be given unless there is a definite indication for it; there are certainly many instances where people have been hospitalized for reactions to rabies vaccine when they had never even been

bitten. However, when rabies vaccine is definitely indicated, we would like to be able to use a product which is incapable of producing this reaction. At the present time, the only readily available way to reduce the possibility of occurrence of this complication is the use of a rabies vaccine made from duck embryo.* This contains a minimum of nervous tissue, and experimental production of allergic encephalitis with it is usually unsuccessful. Therefore it is much less likely to produce complications in man although it has not been used long enough in large enough groups of people to prove this. The vaccine is made from virus grown in a duck embryo and then killed by appropriate chemical treatment. Since the vaccine is marketed in a dry form, it has the added advantage of greater stability.

It has been found that people who have had rabies vaccine given to them as long as 25 years ago respond today after a single dose of vaccine with a booster type of rise in serum antibody levels. Attempts have recently been made to take advantage of this booster effect in groups that are exposed repeatedly by administering a course of vaccine in advance. At the time of exposure, one or two booster doses of vaccine will cause a rapid enough antibody response to prevent the disease. Thus far, a number of veterinarians have been immunized with either brain tissue Semple type killed vaccine, live virus chick-embryo vaccine which is used in dogs, or duck-embryo vaccine. Current practice is to give three doses five days apart and then another booster dose a month later. One month after the booster dose, it is recommended that these individuals have their blood tested for specific antibody response. If there is an adequate antibody response from the primary course of immunization, at a subsequent rabies exposure they are justified in taking only one or at the most two booster doses of vaccine five days apart. For individuals who have not had a determination of circulating antibodies and therefore are not sure that they had a successful primary immunization, the full course of vaccine must be given.

A few general principles about rabies prophylaxis can be laid down. First of all, we feel that a breaking of the skin is necessary in order to constitute an exposure to rabies. In other words, a lick on the sound skin even by a proven rabid dog is not considered an exposure to rabies. This statement is based on 30 years experience in the state of Georgia which has been making its own vaccine. Since the vaccine is given without cost, the state has control over who gets it. They have withheld it from people with exposure to saliva on the sound skin; in over 30 years they have yet to have a case of rabies develop in people who have been thus exposed to

* Manufactured under the name "Rabies Vaccine (Duck Embryo), Dried Killed Virus" by Eli Lilly and Company.

known rabid animals. However, if sound unbroken mucous membrane is licked by a rabid dog, this must be considered an exposure since experimentally it is possible to infect animals occasionally, although not very efficiently, by introducing the virus onto the sound mucous membranes. Scratches by known rabid animals must be considered as exposure because of the possibility that the claw was contaminated at the time of the scratch.

An obvious fact is that it is not possible to make a scientific decision concerning rabies prophylaxis in a human being unless we have the animal that did the biting. If the animal escapes or cannot be identified, only general principles can be stated, and these include an estimate of how much rabies there is in the area. In England or Scandinavia there has not been any rabies in animals for years. But in Georgia or in West Virginia, or in any other state where rabies has been recently reported, there is a good chance that the biting animal might have had rabies; therefore we must bend over backwards to give treatment.

Another general principle which should be emphasized is that there is reason to think that children and younger animals are more susceptible to rabies than adults and older animals. Also, people who are severely bitten are more likely to contract rabies than those who get only a superficial bite. Furthermore, there is some reason, although it is not very well documented, to think that bites about the head and neck are more likely to result in rabies than those on the extremities. Certainly this is true of the experience in Iran where there has been almost never a vaccine failure in patients bitten away from the head and neck, while of those bitten about the head and neck, 40 to 50 per cent died in spite of vaccine treatment. In an area where rabies is in the dog population or in the wild animal population, even though the biting animal is known, is under surveillance and appears healthy, the feeling may be that something should be done in the case of a severely bitten child. In those situations, we recommend that two or perhaps three daily doses of vaccine should be given, but no more than that as long as the animal stays healthy. Two or three doses are not enough to produce allergic encephalitis; yet a basic immunity has been established by introducing antigen early. If the animal subsequently develops symptoms and there is no doubt that he has rabies, a full course of vaccine can then be given.

Two other principles should be mentioned. First, there is less likelihood that an infectious dose of virus will be delivered to the wound if the teeth have gone through the clothing than if they did not, but we can never be sure, and certainly cannot base our decision on that. Likewise, even if the biting dog has been vaccinated against rabies as recently as six months ago, we recommend ignoring the history of vaccination in the dog in making a decision concerning what to do about the human. The vaccine in dogs is

not 100 per cent effective and we can never be sure in which dog it has failed.

What per cent of people bitten by a rabid animal and not treated will develop rabies? Fortunately, man is apparently not so susceptible to rabies as some other species such as foxes, skunks, and cows. The only available data were published in the pre-Pasteur days. In one episode in Germany, a large group of people was bitten by one rabid dog over a period of 24 hours, and 75 per cent of them died of rabies. In almost the same situation in England, 20 per cent died. One recent instance in Iran involved a group of people bitten by a rabid wolf. These people were not treated until the sixteenth or seventeenth day after exposure, when the first case of rabies developed. Treatment starting that long after exposure, of course, is the same as no treatment, and about 45 per cent of these people died.

Should rabies antiserum be given routinely at the same time as the vaccine? This depends on the local situation. If the dog is known, under surveillance, perfectly normal at the time he did the biting, and in an area where there is not much rabies in dogs, the inclination would be not to give antiserum together with the vaccine, although there is certainly no contraindication to giving it. Of course, antiserum itself also is not without danger. Since it is horse serum it can cause serum sickness in about 20 per cent of people to whom it is given. In addition, the antiserum is expensive and consequently will not be used indiscriminately. If there is a moderate amount of rabies in the area and a severe exposure occurs in a child, both antiserum and the first few doses of the vaccine should be given; further treatment should be withheld while the animal is under surveillance.

Clinical Pathological Conference

FERNANDO R. LEYVA, M.D.*
E. CLARENCE RICE, M.D.†

PRESENTATION OF CASE

This 34 month old white girl was admitted to Children's Hospital with a history of vomiting of two days' duration. A slight cold had been noted

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at the onset. There had been no diarrhea. The admitting physician noted evidence of dehydration and commented in the hospital record concerning the high temperatures recorded in the city during the patient's illness. Previous to her admission the private doctor had given her an intramuscular injection of penicillin.

The patient had been a poor eater since 3 months of age; she had walked at 14 months and had talked at 24 months of age. Three months prior to this admission she had undergone resection of the lower lobe of her left lung at Children's Hospital because of bronchiectasis and a lung abscess. *Staphylococcus aureus* was cultured from the abscess. The history given at the time of the previous admission stated that there had been no symptoms other than a nonproductive cough of 18 months' duration.

Examination of the patient following admission disclosed a critically ill, dehydrated child, with cyanosis of the lips, hands, and feet, whose respirations were shallow and at the rate of 100 per minute. Wheezes were heard over the left lower chest anteriorly. The lower border of the liver was felt 1 cm. below the costal margin. The abdomen was soft.

The blood carbon dioxide combining power on admission was 9 milliequivalents per liter and rose to 14.5 milliequivalents per liter four hours later following the intravenous administration of electrolyte-containing solutions. The results of any other laboratory examinations which may have been done are not available.

Therapy consisted of oxygen and the intravenous injection of sodium lactate and calcium gluconate solutions. The patient's condition deteriorated rapidly and she died five hours after admission.

DISCUSSION

Dr. Leyva:

This appears to have been a fulminating illness beginning two or three days before death and characterized by persistent vomiting, severe dehydration, circulatory collapse and death occurring in a 34 month old child.

There was no history of convulsive disorder, fever, diarrhea, or any obvious sign of infection associated with this child's fatal illness. Moreover, the child had enjoyed excellent health following an uneventful lobectomy of the lower lobe of her left lung for bronchiectasis at 30 months of age.

The first question that comes to mind after reading the protocol is whether the fulminating death of this child is related to her previous disease, namely, bronchiectasis, or if on the other hand, it represented an unrelated process. It seems to me that two clinical approaches would ordinarily be

possible in the discussion of a case of this sort. One would be to review the causes and complications of bronchiectasis in infancy to see if they fit with the findings in this child. The second approach would be clinical speculation of all possible differential diagnoses based on the meager information and findings given at the time of admission. This last approach I cannot choose because of the formidable lack of facts necessary to base a logical discussion. Of course, I do appreciate the fact that there was not much time to perform many tests due to the patient's critical condition. Although I accept the protocol as is, I would like to ask Dr. Rice two pertinent questions by which I hope to find valuable information. The first question is about the report on the x-ray films previous to the lobectomy, and the other is about the time of the year in which this child died.

Dr. Rice:

Roentgenograms of the lungs just prior to the lobectomy described "a shadow in the medial half of the left chest extending from the third interspace anteriorly near the mediastinum." A bronchogram revealed "a large 1½ by 1½ inch space in the medial aspect of the left lower lobe filled with lipiodol, with a moderate degree of bronchiectasis in this region and a very early degree of bronchiectasis in the right lower lobe. The possibility of lung cyst or abscess of the left lower lobe is suggested."

As for the second question, admission was in July and was during a heat wave.

Dr. Leyva:

In summary, we have a 34 month old child admitted to the hospital during a hot day in the month of July, in critical condition and almost comatose. The positive findings were severe dehydration which failed to respond to intravenous fluid replacement, cyanosis of the lips, feet, and hands, respiratory distress and a few wheezes heard over the left chest. On the negative side of the history is the absence of diarrhea, fever, or associated infection. There is no mention of neurological findings or a spinal tap, thus speaking against a cerebral complication of bronchiectasis such as a brain abscess or acute meningitis. Apparently one of the causes of this patient's severe dehydration was due to loss of water and salt through vomiting and her failure to ingest an adequate amount of fluid. We all know that such a situation in a child may produce marked electrolyte imbalance which is sometimes irreversible. Persistent nonobstructive vomiting is by far more common than that resulting from obstructive lesions of the gastrointestinal tract. I do not believe that one can consider such diagnoses as intussusception, volvulus, and peritonitis.

On the other hand, acute gastritis or gastroenteritis of undetermined origin, cyclic vomiting and heat prostration should be seriously considered.

It was very enlightening to me to review the causes of bronchiectasis in infancy, because there I found that besides congenital pulmonary cyst, tuberculosis, and chronic nonspecific bronchitis, one should consider fibrocystic disease of the pancreas. Likewise the absence of digestive symptoms or even of pancreatic achylia does not necessarily rule out the diagnosis of fibrocystic disease. Such cases have been recently demonstrated with the aid of the sweat test.

If I am correct in assuming that the etiology of this child's bronchiectasis is secondary to fibrocystic disease, the time of the year and the way in which she died make it possible to entertain a unitary explanation of this child's death. The sequence of events in this child's last illness could be explained as an acute salt loss through the sweat, aggravated by continuous vomiting, thus producing progressive dehydration, cardiovascular collapse, coma and death. These symptoms are largely due to pure salt depletion with contraction of the extracellular space. This syndrome was first described by Dr. Andersen in 1952 when she reported 6 cases of "heat prostration" occurring in patients with fibrocystic disease of the pancreas during the hot months of summer.

I do not know from the history how much sodium chloride this child had lost through the sweat, but whatever the amount, the persistent vomiting set up a vicious circle with further loss of water and salt, contraction of the extracellular space, and finally the vascular collapse which is usually the cause of death.

My final diagnosis is:

1. Bronchiectasis secondary to fibrocystic disease of the pancreas.
2. Acute salt depletion with secondary cardiovascular collapse and death.

May I add that I would not have dared to offer this explanation of the child's illness had Dr. Rice said that the child died in the winter months.

Dr. Rice:

Dr. Leyva's deductions are correct. It is interesting that this child went to operation and came to autopsy without anyone writing on the chart that he suspected that the patient had cystic fibrosis of the pancreas, although the resident, in writing up her summary, made an important observation, viz., that this patient was admitted to the hospital in July during a very hot period. Whether she had in mind this diagnosis, I do not know; she did not write it down.

At autopsy, the diagnosis of cystic fibrosis of the pancreas was made. On opening the chest, we found the left pleural cavity to be nearly obliter-

ated by fibrous adhesions. Underneath the thickened pleura the remaining lung was rather red. The right lung was voluminous, pink in color and somewhat emphysematous. When the bronchi were cut, those on the right were found to be dilated and filled with a thick tenacious mucopurulent material from which *Staphylococcus aureus*, coagulase positive, was isolated. There were also multiple miliary abscesses scattered throughout both lungs, in addition to emphysema, atelectasis and bronchiectasis. The bronchial lymph nodes were enlarged. The heart was moderately enlarged, as was the spleen. The liver did not disclose anything remarkable. The pancreas weighed 14 Gm. and grossly did not show enough to suggest the diagnosis of cystic fibrosis of the pancreas. The gross description states that the ducts were patent. Microscopically this organ showed very marked changes in that there was a great deal of fibrosis and atrophy of the acinar tissue with only remnants of the original structures remaining. The islet tissue remained and apparently was unchanged. The ducts were filled with inspissated pink staining proteinaceous material.

The final diagnoses were cystic fibrosis of the pancreas, bronchiectasis, multiple abscesses of the lung, emphysema, and obliteration of the left pleural cavity due to fibrous adhesions, the latter being secondary to the surgical removal of the lower lobe of the left lung.

Here we have a patient with cystic fibrosis of the pancreas in whom the gastrointestinal symptoms were minimal. Although the child had a poor appetite from the third month of life, according to the chart there had never been any history of diarrhea, voluminous stools, or distension of the abdomen.

This case does illustrate many things of which pathologists have gradually become aware. In this connection meconium ileus was found to be associated with fibrotic and atrophic changes in the acinar tissue with inspissated material in the ducts of the pancreas. Older children with similar histological changes in the pancreas often had histories of inability to digest their food, and often developed pot bellies and were emaciated. Previously they had been diagnosed as having congenital steatorrhea. As we continued to do more and more autopsies on children with these changes in the pancreas, we noted that the mucous glands of the intestinal tract were prominent and distended. As these children lived longer we found increasing evidence of pulmonary changes dependent on the production of thick tenacious mucus from the bronchial glands which were also similarly distended with secretions. With the blocking of the air passages by the mucus, there came multiple abscess formation, dilatation of the bronchi, and rupture of alveoli with emphysema. From the abscesses *S. aureus* was almost always cultured. We became accustomed to finding this rather peculiar looking lung, with emphysema in one portion, and atelectasis in

others, together with firm areas due to multiple abscess formation. We also noted, as we became more accustomed to these changes associated with cystic fibrosis of the pancreas, changes in the parotid gland where there was evidence of excessive secretion due to hypertrophic changes as noted in the other glands.

Later on we began to make observations which were dependent on biochemical changes in the body. This disease became one no longer representing a condition which was of interest primarily to the pathologist. The biochemist, bacteriologist and pediatrician all have an active interest in the disease, and its diagnosis and treatment.

With patients known to have cystic fibrosis of the pancreas being admitted to the hospital on very hot days, as this patient was, and noted to be in a state of heat prostration, Dr. Dorothy Andersen, knowing something of what was going on biochemically, was able to come to a proper evaluation of the biochemical imbalance, a loss of sodium chloride. The determination of the salt content of the sweat is now an easy method of confirming the diagnosis of cystic fibrosis of the pancreas, and is much simpler than passing a tube into the duodenum, withdrawing the fluid and assaying the enzyme content. Whereas 20 years ago the diagnosis was made almost exclusively in the autopsy room, now it is estimated that only about 5 per cent are diagnosed there. This child was one of those. We see about two to three children with cystic fibrosis of the pancreas at autopsy each year. Dr. Andersen calculates that about one baby in 1,500 births has this condition.

Pulmonary fibrosis with secondary cor pulmonale is one of the more recent findings described in cystic fibrosis. Then there is cirrhosis of the liver which I first thought might be secondary to the cardiac pathology. The cirrhosis is apparently the result of this same secretory abnormality noted elsewhere and is caused by plugging of the bile capillaries. Apparently the cirrhosis may exist for a long time without its presence being known, especially since liver function tests are often normal. One may not realize that the patient has liver disease until the large and firm liver is felt, ascites is present, or the patient vomits blood.

We can expect a number of previously unrecognized or misinterpreted findings in these patients in the future as we are increasingly able to prolong their lives; our new teen-age ward will play a part in this. Pediatricians will note symptoms and findings which previously were never associated with this disease. We have made somewhat similar observations in the juvenile diabetic as his life has been prolonged. As these patients grow older they plot an uncharted course. We do not know what is ahead of us insofar as the pathology of this disease is concerned. The history of this disease is far from being written in its entirety.

The Editor's Column

H.N.S.

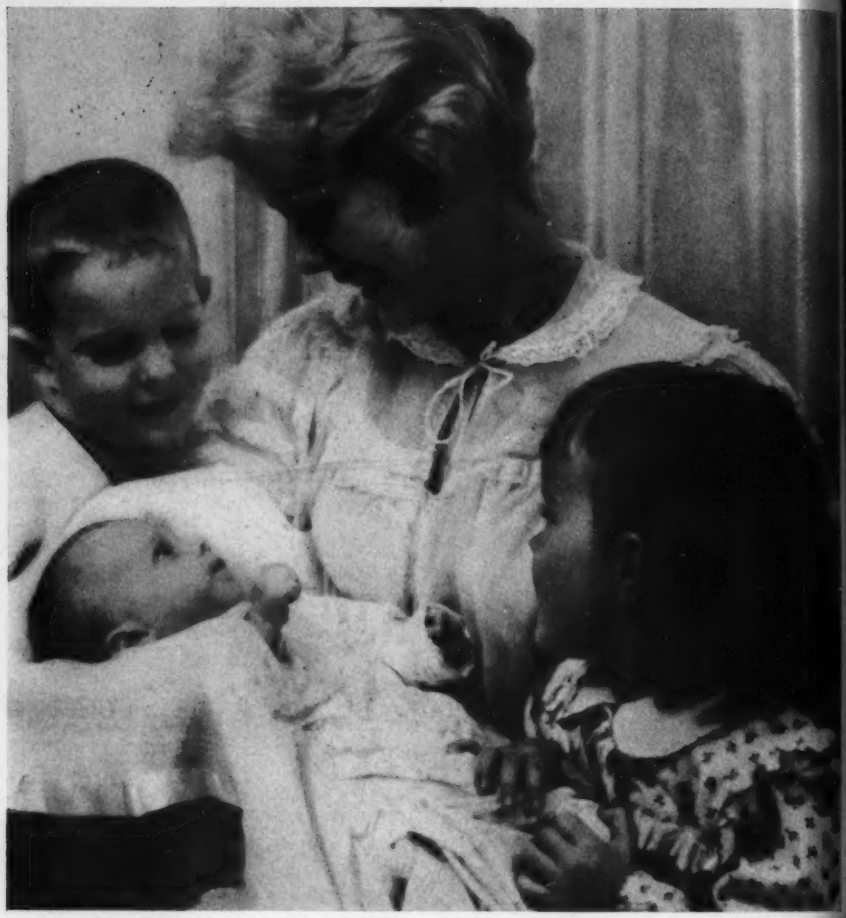
The exchange of medical information between physicians has been, is, and perhaps always will be the most effective means of keeping ourselves "up to date" regarding current medical thought. When confined to its proper setting—the medical journal, lecture hall, scientific meeting, etc.—its value is priceless. However, when it steps beyond these areas, its value diminishes and the price we pay for "off the cuff" discussions within earshot of nonmedical personnel can sometimes be measured only in terms of malpractice litigation and/or unwarranted patient or parent anxiety. This brings up the problem of the Hospital News Service (H.N.S.), the unique self-propagating, unauthorized information medium almost universally present in every hospital.

H.N.S. is a highly organized agency with an efficiency that parallels that of its lay press counterparts. It has mobile units, teams of physicians and nurses who offer day by day bedside reporting for the patient, lest for example, he not be kept *au courant* about the potential toxicity of his present medication. News-in-transit is another special service offered by H.N.S.—an up-to-the-minute discussion of the ups and downs of a patient's course. Appropriately, this is confined to the elevator and is designed to benefit the parents or relatives who are unable to partake of mobile coverage.

The backbone of H.N.S. is the "Coffee Shoppe," the *bureau central*, where prognostic bulletins are issued, complaints registered, and questions answered about any "good" case. It is here where we sparkle in keeping the public informed. In our attempts at being super-efficient members of the H.N.S. staff, we often volunteer patients' names—after all, do we not have a reputation for exactness with detail? How the patients' relatives must love us for our thoughtfulness! The cafeteria, the corridors, the auditorium with doors ajar, even the parking lots are part of H.N.S.'s all-encompassing beat.

What then can be done about this giant organization? Is it already too deep-seated to defy complete repression? Maybe our "wait 'til I tell you about . . ." personalities answer the last question. Perhaps then the solution lies in a merger. A union of H.N.S. with C.L.S. (Closed Lip Service) or even better S.N.S. (Silent News Service) would be a start in the right direction. The resultant corporation, though not as informative, would render a better service than its predecessor—viz., peace of mind not only to our patients and their families, but ofttimes, to ourselves as well.

W. R. O'R.



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